THE CHANGING DRUG DELIVERY PARADIGM

In this article, Beth DiLauri, Director, Strategic Marketing, Self-Administration Injection Systems BD Medical – Pharmaceutical Systems, sets out the fundamental case for the adoption of wearable injectors, outlines the specific barriers they overcome that pens and prefilled syringes cannot, and describes how the design and development of the BD Libertas™ wearable injector platform, paired with the company's unparalleled parenteral delivery device experience and know-how, make BD Libertas™ an attractive proposal for pharma companies seeking a wearable injector.

Recent years have seen ground-breaking advances in pharmaceutical development with increasingly innovative medicines being brought to market. However, the cost of these novel drugs has intensified the pressure to shift medication administration from traditional settings to more cost-effective alternatives. One such alternative is the patient's own home, where novel molecules are now regularly self-administered subcutaneously to treat chronic diseases such as rheumatoid arthritis, multiple sclerosis and dyslipidaemia, among others.

Pharmaceutical companies have worked to develop highly concentrated monoclonal antibodies (mAbs) to improve treatment options for these chronic diseases.[1] At the same time they are looking to ease the burden on patients by reducing injection frequency and enabling home-based delivery. Although this new paradigm holds tremendous potential it also brings new challenges in drug delivery which require innovative solutions to address them effectively.

LIMITATIONS OF CONVENTIONAL DELIVERY SYSTEMS

Historically, delivering the small-molecule drugs developed to treat conditions such as infection, hypertension, and hyperlipidaemia was of little concern, as most of these medicines could be administered orally. Moreover, when the oral route was not an option, most traditional therapies could be easily solubilised and delivered via intravenous (IV), intramuscular (IM), and/or subcutaneous (SC) injection in a relatively small volume of fluid.

Recent developments in biotechnology have produced a plethora of protein-based molecules (e.g. mAbs) that must be injected to achieve their therapeutic effects. To accommodate the volume limitations of current IM and SC delivery methods, manufacturers must concentrate these formulations, thereby creating an additional challenge of high viscosity.[2]

This trend poses a fundamental problem with two possible

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Figure 1: BD Libertas™, a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high-viscosity biologics of up to 50 cP.

"Optimising performance early saves time in the development process and gives us a much better understanding of our users' needs sooner."

solutions, addressed individually or together: 1) increase the injection volume; or 2) increase the injection duration. While these options may be feasible for IV administration, they pose significant impediments to SC delivery, especially when administered by a caregiver or a patient themselves. Practically speaking, humans have a finite ability to self-inject over long periods with traditional delivery devices, as factors such as fatigue, concentration, and the urge to move eventually cause their ability to hold the injection device steadily in place to waver. Physiologically, the SC tissue has a limited physical and absorptive capacity for a rapid influx of large volumes (e.g. >10 mL),[3] and associated injection pressure may lead to drug leakage and injection pain.[4–6] Thus, the clear majority of commercially-available delivery devices (i.e. prefilled syringes and auto-injectors) are designed to administer small drug volumes (≤2 mL) in under 15 seconds.

WEARABLE INJECTORS PRESENT A SOLUTION

Wearable injectors are delivery systems that adhere to the body to administer larger volumes (more than 2 mL) of drug subcutaneously over an extended period. For more than a decade, numerous pharmaceutical and medical device companies have led development efforts to bring wearable injectors to market, including the BD Libertas™ large-volume wearable injector (see Figure 1). While there is variability amongst products, all wearable injectors provide a reservoir for the medication, a cannula for delivery to the tissue, adhesive to fix the device to the patient's skin (Figure 2), and a drive system to deliver the appropriate drug volume.

Figure 2: Wearable injectors provide a drug reservoir, cannula , and adhesive to fix the device to the patient's skin.

Wearable injectors effectively address the volume and viscosity challenges of prefilled syringes and auto-injectors, allowing highly-concentrated drugs to be diluted into larger volumes and administered over longer periods (minutes rather than seconds) without saturating the SC space. Although the potential benefits of these delivery systems are numerous, perhaps the most notable is the ability to self-administer high-volume, high-viscosity drugs in a non-clinical setting.

THE VALUE OF EXPERIENCE

Like all drug delivery devices, a successful wearable injector must be designed to meet the needs of a variety of healthcare stakeholders. Most importantly, it must meet patients' needs for simplicity in the non-clinical setting.

These devices must also meet the pharmaceutical manufacturer's needs for a solution that offers proven, well-integrated components that fit into existing fill/finish processes. This is a significant requirement that demands partners with experience in producing drug delivery devices.

As a leader in delivering high-quality medical devices for over 100 years, BD can leverage its broad experience to meet these requirements effectively and

Figure 3: The BD Libertas™ device has a unique fluid transfer valve built in, enabling the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility.

successfully introduce new drug delivery systems. "BD's extensive expertise in medical device development, primary containers and needles allows for the seamless addition of a wearable injector to any pharmaceutical partner's portfolio," said Kevin Kelly, Vice-President of BD Medical – Pharmaceutical Systems' Self-Administration Injection Systems business.

BD LIBERTAS™, THE NEXT GENERATION OF WEARABLE INJECTORS

BD Libertas™ is a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high-viscosity biologics of up to 50 cP. Its unique design and interface were informed by extensive preclinical and clinical research, resulting in a device with minimal steps and little complexity.

Simplicity in Design

Unlike some other wearable injectors, BD Libertas™ does not require user assembly or filling, significantly reducing the potential for human error and contamination. Devices that require user assembly and filling introduce the potential for dropping (and breaking) the primary container, incorrect assembly, touching aseptic areas, and increasing patient and caregiver confusion. Conversely, BD Libertas™ comes completely pre-assembled and ready to use out of the package, eliminating the greatest source of contamination: human interaction.

> "BD Libertas™ incorporates BD Neopak™ primary container technology and employs the same cannula technology found in BD's world-class needles."

"The convenient presentation is enabled by a unique fluid transfer valve built into the injector. The valve enables the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility [Figure 3]," explains Peter Quinn, BD's Wearable Injector Product Platform Leader.

Pioneering Injection Research

BD has conducted rigorous preclinical and clinical research to ensure effective SC delivery of large-volume injections. The Translational Sciences Center of Excellence at BD Technologies has partnered with BD Pharmaceutical Systems to provide *in vivo* testing of BD Libertas™. This collaboration provides valuable insights to impact device design directly, and offers early information on performance in a living system that is not easily replicated on the bench.

Approximately 40 preclinical studies were conducted to characterise the tissue response to large-volume SC deposition, investigate effects that could influence patient perception of the device, and optimise design and system components. These studies evaluated device performance across a broad range of injection conditions that pharmaceutical companies may need to deliver their molecules (e.g. varying viscosities, flow rates, injection times, or body locations). "One extraordinarily valuable aspect of *in vivo* testing is the ability to develop a model that is a good predictor of human outcomes. With rigorous preclinical testing, we can quickly gain the information we need to understand delivery dynamics and device footprint, and optimise device performance before we move on to human testing," commented Natasha Bolick, Manager, BD Technologies.

BD has used this extensive preclinical research to inform four clinical studies. Two of these studies were specific to BD Libertas™ design component optimisation, while the remaining were large-volume injection studies that employed a surrogate system to mimic BD Libertas™ delivery. Through these clinical studies BD gained a comprehensive understanding of the large volume SC injection experience across a variety of injection conditions and valuable insight into patient acceptance and preference. "It's important that we provide the best possible

"Purely mechanical systems provide reliable and known mechanisms for administration, which may help to reduce risk and increase reliability. In contrast, electromechanical devices typically require pumps, which may introduce technical complexities and unknown sources of error."

experience for our end users," Bolick emphasised. "Optimising performance early saves time in the development process and gives us a much better understanding of our users' needs, sooner."

Integrating Trusted Components

Paired with these novel innovations and capabilities, BD leverages the technologies it already delivers to pharmaceutical manufacturers by the millions every day. BD Libertas™ incorporates BD Neopak™ primary container technology and employs the same cannula technology found in BD's world-class needles. "Libertas was purpose built to provide a complete solution, anticipating both patient and manufacturer needs," said Theresa Bankston, Associate Director, Technical Services.

Benefits of Mechanical Systems

A mechanical drive system, like that found in BD Libertas™, provides a robust, industry-tested method of delivering medication. Purely mechanical systems provide reliable and known mechanisms for administration, which may help to reduce risk and increase reliability. In contrast, electromechanical devices typically require pumps, which may introduce technical complexities and unknown sources of error.

Moreover, purely mechanical devices may deliver more comfortable injections compared with electromechanical devices, as they are responsive to tissue back-pressure. As fluid diffuses into the subcutaneous space, pressure in the tissue slowly builds, which may induce pain at the injection site. When this occurs during mechanical delivery, the device responds by naturally slowing the medication delivery toward the end of the injection, reducing the potential for pain. Conversely, electromechanical devices are designed to deliver medication at a constant delivery rate regardless of tissue back-pressure. A final advantage of purely mechanical devices is simply the absence of electronics from the core device. This is particularly beneficial when it comes to device disposal.

Customisation Options

BD offers the ability to adapt several aspects of the BD Libertas™ device, including the look and feel and injection volume, while keeping the core footprint standardised. It will be available in two volume formats, 2-5 mL and 5-10 mL, both housed within a similar device design.

The BD Libertas™ design features customisable outer-facing components, enabling further flexibility without impacting on the functionality of the device. For example, grip and button colours can be changed to reflect branding. The device's outer cover can also be modified with components that contain enhanced functionality. In this way, any BD Libertas™ device can be easily modified or upgraded as needed, without any changes to the core device module.

Flexibility to Become "Smart"

The BD Libertas™ design is future-proofed to meet evolving industry trends. More developers are looking to enhance the injection experience by incorporating "smart" features and connecting with the digital health ecosystem (Figure 4). Although a limited number of commercially-available drug delivery devices currently have smart features, connected devices are poised to become the norm over the next 5-10 years.[7]

According to Kelly, BD believes that smart devices should encompass both local and global connectivity: local, in that a smart device should help facilitate better interactions with individual users; and global, in that the device should enable communication with others about its state and usage. BD has taken this approach in the development of BD Libertas™, while also recognising that not every situation requires the same degree of connectivity.

BD Libertas™ was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device. In this way, one platform can accommodate both local and global connectivity for the same molecule or across molecules within one customer. BD Libertas™ truly offers a platform solution for pharmaceutical companies.

Figure 4: BD Libertas™ was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device.

SUMMARY

Wearable injectors present a comprehensive solution to the challenge of delivering SC injections of increasing dosing volumes and viscosities in non-clinical settings. Introducing robust, innovative technologies will allow more patients to enjoy the convenience of injecting at home. In addition, the ability to accommodate new formulations with higher volume and/or viscosity will enable less frequent injections, improve the patient experience, and potentially increase adherence to therapies.

Bringing new injection technologies to market introduces complexities that pharmaceutical companies must consider as they select the right wearable injector platform for their portfolio. However, experience in providing prefillable injection technologies, delivering well-integrated primary container and device systems, and working with partners who understand the intricacies of delivering drugs into the subcutaneous space all help to increase peace-of-mind for pharmaceutical companies in bringing combination products to market.

BD Libertas™ represents the newest addition to BD's platform of integrated device components to support the development of combination products to enable a variety of options for delivering self-administered biologics.

BD Libertas™ is a product in development; some statements made are subject to a variety of risks and uncertainties.

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Beth DiLauri is Director, Strategic Marketing at BD Medical – Pharmaceutical Systems, responsible for developing portfolio strategies and leading commercialisation for self-injection devices with the Pharmaceutical Systems business. She has dedicated her 18-year career at BD to developing and executing portfolio strategies based on deep market and customer insights, across multiple segments of the healthcare industry including pharma/biotech, medical devices, diagnostics and healthcare IT. Prior to BD, DiLauri was responsible for business development at Transcend Therapeutics, a venture-backed development-stage pharmaceutical company, from inception through its Initial Public Offering on the NASDAQ in 1997. She received an MBA from the Tuck School of Business at Dartmouth College (Hanover, NH, US), and a Bachelors' degree in Psychology from Boston College (MA, US).

Based on an article that originally appeared in ONdrugDelivery, September 2017 (Issue 78), pp 16-20.

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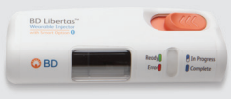
BD Libertas™ Wearable Injector



BD Libertas™ Wearable Injector with Smart option

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GOOD DESIGN

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BD Libertas™ Wearable Injector and BD Libertas™ Wearable Injector with Smart option are products in development; some statements made are subject to a variety of risks and uncertainty.